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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/700,158	11/03/2003	Ting-Fen Tsai	5223-4	3816

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EXAMINER	
MONTANARI, DAVID A	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 05/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/700,158	TSAI ET AL.	
	Examiner	Art Unit	
	David Montanari	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11/30/2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. David Montanari, Ph.D, AU 1632, has taken over prosecution of this case.

2. Applicant's arguments filed 2/16/2005 have been fully considered but they are not persuasive.

3. The rejection of claims 1-8 under 35 USC 112, 1st paragraph as lacking enablement made in the office action mailed 10/12/2004 has been withdrawn in view of the new rejection below.

4. The rejection of claims 1-8 under 35 USC 112, 1st paragraph as lacking written description made in the office action mailed 10/12/2004 written description has been withdrawn in view of applicant's arguments.

5. The rejection of claims 1, and 7-8 under 35 USC 112, 2nd paragraph made in the office action mailed X is withdrawn in view of applicant's amendments to the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not teach how one of skilled in the art at the time of filing would use a transgenic mouse comprising a first transgene expression cassette comprising a mouse agouti cDNA operably linked to a human

keratinocyte specific K14 (K14-Ag) promoter, a second transgene expression cassette comprising RNA polymerase II large subunit (Pol II) promoter, and a chicken beta-globulin HS4 insulator or a transgenic mouse comprising a first transgene expression cassette comprising the mouse cDNA operably linked to the mouse tyrosinase (Tyr) promoter, a second transgene expression cassette comprising the Pol II promoter, and a chicken beta-globulin HS4 insulator. The claimed invention relates to transgenic mice that comprise a vector comprising a transgene of interest operably linked with a Pol II promoter, a visible reporter gene (K14-Ag), and chicken beta-globulin HS4 insulator. The specification teaches seven transgenic mice: the 1st comprising K14-Ag alone, the 2nd comprising K14-Ag, and the antibiotic resistance gene Neomyocin (Neo) operably linked to the Pol II promoter (Pol II-Neo), the 3rd comprising K14-Ag, Pol II-Neo with 4 copies of the HS4 insulator placed at the 5' end of the transgene expression cassette, the 4th comprising K14-Ag, Pol II-Neo with 2 copies of the HS4 insulator placed at the 5' end of the transgene expression cassette, the 5th comprising K14-Ag, Pol II-Neo with 2 copies of the HS4 insulator placed at the 3' end of the transgene expression cassette, the 6th comprising K14-Ag, Pol II-Neo with 2 copies of the HS4 insulator placed at the 3' end of the transgene expression cassette, wherein the insulator is in the opposite orientation relative to the first and second expression cassettes (mice 1-6 illustrated in Fig. 1), and the 7th comprising mouse cDNA operably linked to the mouse Tyr promoter, the enhanced green fluorescent protein gene (eGFP) operably linked to the Pol II promoter with 2 copies of the HS4 insulator placed at the 3' end of the transgene expression cassette, wherein the insulator is in the opposite orientation relative to the first and second expression cassettes (Fig. 5 A-E). The specification teaches that the mice comprising the Pol II-Neo transgene, high levels of Neo mRNA was detected in all of the

transgenic lines exhibiting coat color effects (pg. 22 lines 3-5), that there was no correlation between strength of coat color phenotype and levels of Neo expression (pg. 22 lines 5-6), and that in one of three lines that exhibited no coat color change, Neo expression was detected (pg. 22 lines 8-10). The specification further teaches that mice comprising Pol II-eGFP exhibited green fluorescence when excited with GFsP light in thirteen of fourteen transgenic mice (pg. 23 parag. 2 lines 2-4), and that four of the thirteen mice exhibited a coat color (distinct light tan coloration) effect along with eGFP fluorescence (pg. 23 parag. 2 lines 4-6). While the specification has demonstrated that mice comprising a first transgene expression cassette comprising a mouse agouti cDNA operably linked to a human keratinocyte specific K14 (K14-Ag) promoter, a second transgene expression cassette comprising RNA polymerase II large subunit (Pol II) promoter, and a chicken β-globulin HS4 insulator or a transgenic mouse comprising a first transgene expression cassette comprising the mouse cDNA operably linked to the mouse tyrosinase (Tyr) promoter, a second transgene expression cassette comprising the Pol II promoter, and a chicken β-globulin HS4 insulator do have a change in coat color when a transgene of interest is expressed that can be identified visually. However the specification fails to teach any use for said mice expressing any transgene of interest operably linked to the Pol II promoter.

The art teaches that the Pol II promoter is ubiquitous and drives expression of a transgene in all cell types (Ahearn, pg. 10695 col. 1 parag. 2 lines 8-11 and pg. 10703 col. 1 parag. 2) Thus, Pol II would regulate expression of the transgene in all cells and tissues of the mouse. There is no disclosed use in the specification for universal tissue expression of any transgene in the transgenic mouse. The question to be asked is "how would such a mouse be used?" The answer

is "the specification provides no such guidance on using this mouse." In particular, the specification discloses the mouse to express a neomycin resistance gene from the Pol II promoter. A patentable use for such a mouse is not provided in the specification, and none is apparent. Further one skilled in the art at the time of filing would find that expression of a transgene of interest and getting a desired phenotype are highly dependent on the selection of an appropriate promoter. Gotz et al. teach that transgenic mice comprising 4-repeat human tau under the control of the human Thy-1 promoter showed early changes associated with the development of neurofibrillary lesions in Alzheimer's disease (pg. 127 parag. 4 last sentence). Gotz continues that transgenic mice comprising 4-repeat human tau under the control of the human Thy-1.2 promoter had approximately fivefold higher levels of Tau mRNA, and was used because the amyloid plaques in transgenic mice expressing familial Alzheimer's disease mutations of human amyloid precursor protein was directly correlated with the expression level of the transgene (pg. 127 last parag.). Schneider et al. further teach that different promoters significantly alter the phenotypic characteristics in insulin-like growth factor-binding (IGFBP) transgenic mice. IGFBP transgenic mice using the metallothionein-1 promoter had abnormal brain development and increased tolerance to ethanol (pg. 631 col. 2 parag. 2 lines 2-5 and table 3), IGFBP transgenic mice using the phosphoglycerate kinase promoter had impaired brain development, reduced birth weight, postnatal growth retardation, altered glucose homeostatis, and pancreas structure (pg. 632 col. 1 parag. 1 lines 1-6 and table 3), and IGFBP transgenic mice using the human alpha-1-antitrypsin promoter had reduced brain weight with several alterations, reduced body weight gain, glucose tolerance affected, impaired fecundity, proteinuria, and glomerulus lesions (pg. 632 col. 1 parag. 2 and table 3). Thus, expression from Pol II is not going

to provide a mouse that has a use as a disease model. Again, the specification does not provide an enabled, patentable use for the mice of the claims. There is no guidance or suggestion for a use and none is apparent. Given the present disclosure and cited teachings, one skilled in the art would have been required to complete an undo amount of experimentation without a predictable degree of success to use the mice claimed comprising the Pol II promoter.

Further it is noted by the examiner that the specification discloses eleven founder transgenic mice comprising Ag cDNA operably linked to the K14 promoter without the Pol II promoter and chicken β-globulin HS4 insulator and only one of the eleven had a detectable coat color phenotype (pg. 17 parag. 3 lines 1-5 and fig 1A). This particular expression cassette demonstrates a lack of reproducibility.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Montanari whose telephone number is 1-571-272-3108. The examiner can normally be reached on M-F 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 1-571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 1-571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deborah Crouch

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